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EXAMINER	
STRZELECKA, TERESA E	

ART UNIT	PAPER NUMBER
1637	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/034,451	MIRKIN ET AL.	
	Examiner	Art Unit	
	Teresa E Strzelecka	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 September 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *37-72* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *37-72* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *8/12/04;11/4/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. This office action is in response to an amendment filed September 27, 2004. Claims 3-19, 32-34 and 36 were previously pending. Applicants cancelled claims 3-19, 32-34 and 36, and added new claims 37-72. Claims 37-72 are pending and will be examined.

2. Applicants' claim cancellations obviated the following rejections: rejection of claims 3-5, 7, 10 and 36 under 35 U.S.C. 102(e) as anticipated by Abbott et al.; rejection of claims 8 and 9 under 35 U.S.C. 103(a) over Abbott et al. and Mirkin et al.; rejection of claims 11-19 under 35 U.S.C. 103(a) over Abbott et al. and Mirkin et al.; rejection of claims 32-34 under 35 U.S.C. 103(a) over Abbott et al. and Mirkin et al. The provisional double patenting rejections are rephrased in view of claim cancellations and amendments to the instant application and application No. 10/153,483.

3. This office action contains new grounds for rejection which were necessitated by amendment. Applicants' arguments are addressed in the "Response to Arguments" section below.

Information Disclosure Statement

4. The information disclosure statement (IDS) submitted on August 12, 2004 (10^{th} supplemental) was filed after the mailing date of the non-final office action on March 26, 2004. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner. Reference 2 was considered but it will not be printed, as it is a duplicate of previously submitted reference.

5. The information disclosure statement (IDS) submitted on November4, 2004 (11^{th} supplemental) was filed after the mailing date of the non-final office action on March 26, 2004. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner. References 1, 2 and 45-52 were considered but it will not be printed, as they are duplicates of previously submitted references.

Response to Arguments

6. Applicant's arguments filed September 27, 2004 have been fully considered but they are not persuasive.

A) Regarding the priority date of claims 6-9 and 32-34, now claims 42-45 and 69-71, Applicants argue that the provisional application No. 60/293,861 "... discloses and regonizes the broad utility of the claimed core/shell nanoparticle conjugates". However, claims 42-45 are drawn to core/shell nanoparticle conjugates with metal cores of FePt, FeAu, metal oxide cores or magnetic cores, none of which are mentioned in the provisional application. Further, broad recognition of possible application of a material does not provide basis for specific methods, such as the methods of claims 69-71. Therefore, claims 42-45 and 69-71 have a priority date of the instant application, i.e., December 28, 2002.

B) Regarding the definition of the term "nanoparticle", Applicants argue that the term has been defined in the application No. 09/760,500. However, there is no such definition in the No. 09/760,500. Further, Applicants cite specification on pages 8-13 as providing such a defintion. However, the cited pages and lines contain example of nanoparticle sizes, not the definition of the term "nanoparticle".

Therefore the previously presented interpretation of the term "nanoparticle" is maintained.

C) Regarding the rejection of claims 3-5, 7, 10 and 36 (now amended claims 37, 38, 40, 43, 46 and 72) under 35 U.S.C. 102(b) over Abbott et al., Aplicants argue that the particles of Abbott et al. do not anticipate the claims since Abbott et al. do not teach that the cores of the core/shell nanoparticle conjugates do not exhibit a red shifting and broadening of the plasmon resonance band relative to cores surrounded by alloyed gold shells. However, the absence of red shift of the palsmon resonance is an inherent property of particles obtained by Applicants using reduction of a

gold salt in solution containing cores of the particles. The particles of Abbott et al. are obtained the same way as Applicants' particles, therefore, they are expected to possess the same property of not exhibiting red shift of the plasmon resonance.

As stated in the specification (page 4, lines 32, 33 and page 5, lines 1-8): "In yet another aspect the present invention provides a method for preparation of non-alloying gold core/shell nanoparticles and product produced therefrom. The method of the invention comprises providing an inner nanoparticle core, treating the core simultaneously with a solution comprising a gold salt and a solution comprising a reducing agent, and isolating the core/shell nanoparticles. The method provides for the first time a non-alloying gold shell surrounding a nanoparticle core. These non-alloying gold core/shell nanoparticles exhibit suprising superior spectroscopic properties not found in conventional gold core/shell nanoparticles and can be functionalized with molecules such as nucleic acids and receptors, to produce nanoparticle conjugates that can be used for targeting and detecting target analytes such as nucleic acids, antigens, proteins, carbohydrates and other substances."

> Abbott et al. teach making the core-shell nanoparticles by providing a particulate substrate and electrolessly plating gold onto the particles. The process involves using easily reducible gold salt, such as $Na_3Au(SO_3)_2$ and a reducing agent (col. 37, lines 6-38).
>
> "Any electroless plating solution that can plate a metal onto a particle can be used in practicing this aspect of the invention, however, solutions having certain characteristics are presently preferred. In a presently preferred embodiment, the plating solution comprises an easily reduced metal salt. In a preferred embodiment, a gold plating solution is utilized and the gold plating solution comprises a reducible gold salt. A presently preferred reducible gold salt is $Na_3Au(SO_3)_2$.
>
> In another preferred embodiment, the metal plating solution further comprises a reducing agent. Reducing agents that are useful in this aspect of the invention include, hydroxylamine, oxalic acid, hydrazine, sodium borohydride and formaldehyde. A presently preferred reducing agent is formaldehyde."

Therefore, core-shell particles of Abbott et al. are produced by simultaneously contacting the cores with a solution which contains gold salt and a reducing agent, as described by Applicants, therefore they are expected to possess the same properties as Applicants' core-shell particles, such as the shell being non-alloying.

Further, Applicants showed the absence of red shift in the plasmon resonance for silver cores only, not for any other metal core.

Therefore, the rejections previously presented for claims 3-5, 7 and 10-16 are now applicable to claims 37, 38, 40, 43, 46 and 55-60.

D) Regarding the rejection of claims 8, 9 and 32-34 (current claims 44, 45 and 69-71) over Abbott et al. and Mirkin et al., Applicants argue the properties of particles of Abbott et al., such as the shells being non-alloying and the cores not having their plasmon resonance red-shifted. These arguments were addressed above.

Therefore, the rejections previously presented for claims 8, 9 and 32-34 are applicable to the current claims 44, 45 and 69-71.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 48, 49, 50 and 51 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claims 48 and 49 are indefinite in claim 48. Claim 48 recites the limitation "the gold salt" in line 2. There is insufficient antecedent basis for this limitation in the claim. Claim 37, from which claim 48 depends, does not contain a limitation relating to a gold salt.

B) Claims 50 and 51 are indefinite in claim 50. Claim 50 recites the limitation "the reducing agent" in line 2. There is insufficient antecedent basis for this limitation in the claim. Claim 37, from which claim 50 depends, does not contain a limitation relating to a reducing agent.

Claim Interpretation

9. Applicants did not define the term "nanoparticle", therefore this term is interpreted as a particle of any size.

Claim Rejections - 35 USC § 102

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

11. Claims 37-40, 43, 46-51 and 72 are rejected under 35 U.S.C. 102(e) as being anticipated by Abbott et al. (U. S. Patent No. 6,277,489 B1; cited in the IDS and in the previous office action).

Regarding claim 37, 40, 43, 47-51 and 72, Abbott et al. teach a multilayered material comprising a particulate substrate (= core), a metal film layered onto the substrate (= shell) and a recognition moiety attached to the metal layer (col. 4, lines 22-35). The particulate substrate can be any material, such as metal oxide, for example Fe_2O_3, NiO (col. 10, lines 34-36). The particulate substrate may be any metal, selected according to desired properties, for example, being magnetic (col. 9, lines 55-67; col. 10, lines 1-6, 33-67; col. 11, lines 1-4). The particles can be of any size (col. 9, lines 63-65).

The particulate substrate is coated with a metal layer (= shell), such as gold, silver, platinum, palladium, nickel and copper, with gold being particularly preferred (col. 9, lines 3-13; col. 11, lines 34-55). An organic layer is attached to the metal layer and provides a link to the recognition moiety.

Regarding claim 38, Abbott et al. teach recognition moieties including biomolecules, such as nucleic acids (col. 12, lines 9-25; col. 16, lines 38-54; col. 19, lines 56-59).

Regarding claim 39, Abbott et al. teach oligonucleotides having reactive groups which can bind to nanoparticle (col. 22, lines 66, 67; col. 23, lines 1-5).

Regarding claim 46, Abbott et al. teach at least one layer of the metal coating (col. 11, lines 44-46).

Note regarding rejection of claims 47-51 and 72: these are product-by-process claims, and it is not clear how the method of making a product of claims 47-51 and 72 makes the final product, i.e., a core-shell nanoparticle with oligonucleotide bound to it, different from the product of Abbott et al. (see MPEP 2113).

MPEP 2113 Product-by-Process Claims

PRODUCT-BY-PROCESS CLAIMS ARE NOT LIMITED TO THE MANIPULATIONS OF THE RECITED STEPS, ONLY THE STRUCTURE IMPLIED BY THE STEPS.

"[E]ven though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." In re Thorpe, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985) (citations omitted) (Claim was directed to a novolac color developer. The process of making the developer was allowed. The difference between the inventive process and the prior art was the addition of metal oxide and carboxylic acid as separate ingredients instead of adding the more expensive pre-reacted metal carboxylate. The product-by-process claim was rejected because the end product, in both the prior art and the allowed process, ends up containing metal carboxylate. The fact that the

metal carboxylate is not directly added, but is instead produced in-situ does not change the end product.).

Claim Rejections - 35 USC § 103

12. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

13. Claims 41, 44, 45 and 69-71 are rejected under 35 U.S.C. 103(a) as being unpatentable over Abbott et al. (U. S. Patent No. 6,277,489 B1; cited in the IDS and in the previous office action) and Mirkin et al. (U.S. Patent No. 6,361,944 B1; cited in the IDS and in the previous office action).

> The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art only under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 103(a) might be overcome by: (1) a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not an invention "by another"; (2) a showing of a date of invention for the claimed subject matter of the application which corresponds to subject matter disclosed but not claimed in the reference, prior to the effective U.S. filing date of the reference under 37 CFR 1.131; or (3) an oath or declaration under 37 CFR 1.130 stating that the application and reference are currently owned by the same party and that the inventor named in the application is the prior inventor under 35 U.S.C. 104, together with a terminal disclaimer in accordance with 37 CFR 1.321(c). For applications filed on or after November 29, 1999, this rejection might also be overcome by showing that the subject matter of the reference and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person. See MPEP § 706.02(l)(1) and § 706.02(l)(2).

A) The teachings of Abbott et al. are presented above. Abbott et al. do not teach nanoparticle core being silver magnetic, but they do teach that the metal cores may any metals or may be selected for their magnetic properties.

C) Regarding claims 41, 44 and 45, Mirkin et al. teach nanoparticle-oligonucleotide conjugates used in nucleic acid detection methods (col. 2, lines 6-17). Mirkin et al. teach nanoparticles being silver or magnetic (col. 16, lines 29-32), and Fe_3O_4 core nanoparticles with a silica shell, which can be conjugated to oligonucleotides (col. 33, lines 19-27).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have used magnetic-core of Mirkin et al. in the nanoparticles of Abbott et al. The motivation to do so would have been that oligonucleotides attached to magnetic particles could be removed from solution by application of a magnetic field, allowing easy separation of hybridization products from solution.

D) Regarding claim 69, Abbott et al. teach a multilayered material comprising a particulate substrate (= core), a metal film layered onto the substrate (= shell) and a recognition moiety attached to the metal layer (col. 4, lines 22-35). The particulate substrate can be any material, such as metal oxide, for example Fe_2O_3, NiO. The particulate substrate may be any metal, selected according to desired properties, for example, being magnetic (col. 9, lines 55-67; col. 10, lines 1-6, 33-67; col. 11, lines 1-4). The particles can be of any size (col. 9, lines 63-65).

The particulate substrate is coated with a metal layer, such as gold, silver, platinum, palladium, nickel and copper, with gold being particularly preferred (col. 9, lines 3-13; col. 11, lines 34-55). An organic layer is attached to the metal layer and provides a link to the recognition moiety. Recognition moieties include biomolecules, such as nucleic acids (col. 12, lines 9-25; col. 16, lines 38-54; col. 19, lines 56-59).

The multilayered material may be used to capture a molecule in a purification process or an assay, and the captured molecule may be a nucleic acid (col. 24, lines 13-62). The multilayered material may be used to determine the presence or quantity of an analyte in a sample by contacting

the sample with a multilayered material, forming a complex between a recognition moiety and an analyte and detecting the analyte (col. 31, lines 44-63).

B) Abbott et al. do not teach detection of nucleic acids bound to a surface or hybridization conducted in the presence of magnetic field.

C) Regarding claim 69, Mirkin et al. teach detection of analyte DNA bound to a surface, the method comprsing:

(a) contacting the surface with a solution comprising core/shell nanoparticle oligonucleotide conjugates of claim 37, wherein the nanoparticle core is magnetic, and wherein the contacting takes place under conditions effective to allow hybridization of the core/shell nanoparticle oligonucleotide conjugates with the bound nucleic acid (Mirkin et al. teach contacting nanoparticle-oligonucleotide conjugates with analyte nucleic acid bound to a substrate (Fig. 13A; col. 2, lines 6-17; col. 19, lines 43-50; col. 21, lines 19-59). Mirkin et al. teach nanoparticles being magnetic (col. 16, lines 29-32).);

(b) subjecting the nanoparticle conjugate to an external magnetic field so as to accelerate movement of the nanoparticle conjugate to the surface to promote interaction between the nanoparticle conjugate and the nucleic acid (Mirkin et al. teach application of magnetic field (col. 33, lines 45 and 60, 61).);

(c) removing from the surface any nanoparticle conjugates that have not hybridized with the nucleic acid (Mirkin et al. teach washing unbound nanoparticle conjugates from the substrate (col. 21, lines 60-63).); and

(d) observing a detectable change brought about by hybridization of the nucleic acid with the nanoparticle conjugates (Mirkin et al. teach observing a detectable change brought about by hybridization (col. 22, lines 22-39 and 57-65).

Regarding claim 70, Mirkin et al. teach nanoparticles being magnetic (col. 16, lines 29-32), and Fe_3O_4 core nanoparticles with a silica shell, which can be conjugated to oligonucleotides (col. 33, lines 19-27).

Regarding claim 71, Mirkin et al. teach washing unbound nanoparticle conjugates from the substrate (col. 21, lines 60-63).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have combined magnetic-core particle hybridization of Mirkin et al. with analyte detection assays of Abbott et al. The motivation to do so would have been that oligonucleotides attached to magnetic particles could be removed from solution by application of a magnetic field, allowing easy separation of hybridization products from solution.

14. Claims 52-68 are rejected under 35 U.S.C. 103(a) as being unpatentable over Abbott et al. (U. S. Patent No. 6,277,489 B1; cited in the IDS and in the previous office action) and Mirkin et al. (U.S. Patent No. 6,506,564).

The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art only under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 103(a) might be overcome by: (1) a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not an invention "by another"; (2) a showing of a date of invention for the claimed subject matter of the application which corresponds to subject matter disclosed but not claimed in the reference, prior to the effective U.S. filing date of the reference under 37 CFR 1.131; or (3) an oath or declaration under 37 CFR 1.130 stating that the application and reference are currently owned by the same party and that the inventor named in the application is the prior inventor under 35 U.S.C. 104, together with a terminal disclaimer in accordance with 37 CFR

1.321(c). For applications filed on or after November 29, 1999, this rejection might also be overcome by showing that the subject matter of the reference and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person. See MPEP § 706.02(l)(1) and § 706.02(l)(2).

A) Regarding claim 55, Abbott et al. teach a method for making core/shell nanoparticle oligonucleotide conjugates comprising

(a) providing inner metal-containing nanoparticle cores and non-alloying gold shells surrounding the cores, wherein the cores of the core/shell nanoparticle conjugates do not exhibit a red shifting and broadening of the plasmon resonance band relative to cores surrounded by alloyed gold shells; (Abbott et al. teach providing metal-containing nanoparticle cores (col. 37, lines 5-11; col. 38, lines 16-20; col. 10, lines 33-67; col. 11, lines 1-4). The particles comprise a particulate substrate (= core), a metal film layered onto the substrate (= shell) and a recognition moiety attached to the metal layer (col. 4, lines 22-35). The particulate substrate can be any material, such as metal oxide, for example Fe_2O_3, NiO. The particulate substrate may be any metal, selected according to desired properties, for example, being magnetic (col. 9, lines 55-67; col. 10, lines 1-6, 33-67; col. 11, lines 1-4). The particles can be of any size (col. 9, lines 63-65).

The particulate substrate is coated with a metal layer, such as gold, silver, platinum, palladium, nickel and copper, with gold being particularly preferred (col. 9, lines 3-13; col. 11, lines 34-55). Since the core/shell nanoparticles of Abbott et al. are prepared in the same way as the core/shell nanoparticles of the instant application, Abbott et al. inherently teach non-alloying gold shells and absence of red-shifted plasmon resonance of the core.);

(b) contacting the oligonucleotides with the isolated core/shell nanoparticles in a first aqueous solution for a period of time sufficient to allow some of the oligonucleotides to bind to the

nanoparticles (Abbott et al. teach attachment of a reactive moiety and recognition moiety to the particles (col. 38, lines 22-32; col. 21, lines 32-47). One of the contemplated recognition moieties is nucleic acid (col. 19, lines 57; col. 22, lines 66, 67; col. 23, lines 1-5).).

Regarding claim 56, Abbott et al. teach oligonucleotides having reactive groups which can bind to nanoparticle (col. 22, lines 66, 67; col. 23, lines 1-5).

Regarding claim 64, Abbott et al. teach treating the inner metal-containing nanoparticle cores simultaneouslv with a solution comprising a gold salt and a solution comprising a reducing agent under conditions that produce a non-alloying gold shell surrounding the nanoparticle cores (Abbott et al. teach treating the core particles with a solution containing a gold salt, such as such as $Na_3Au(SO_3)_2$ and a reducing agent (col. 37, lines 6-38).

Regarding claims 67 and 68, Abbott et al. teach sodium borohydride, $NaBH_4$ (col. 37, line 36).

B) Abbott et al. do not teach addition of salt to the oligonucleotide-nanoparticle solution, or oligonucleotide densities of at least 10 picomoles/cm^2, or least 15 picomoles/cm^2, or from about 15 picomoles/cm^2 to about 40 picomoles/cm^2.

C) Regarding claim 55, Mirkin et al. teach attachment of oligonucleotides to surfaces of gold nanoparticles by the process comprising:

(b) contacting the oligonucleotides with the isolated core/shell nanoparticles in a first aqueous solution for a period of time sufficient to allow some of the oligonucleotides to bind to the nanoparticles (Mirkin et al. teach contacting oligonucleotides with nanoparticles in water (= first aqueous solution) to allow some of the oligonucleotides to bind to the nonoparticles (col. 48, lines 24-34.)).

(c) adding at least one salt to the aqueous solution to create a second aqueous solution (Mirkin et al. teach adding at least one salt to the aqueous solution to create a second aqueous solution (col. 48, lines 35, 36).); and

(d) contacting the oligonucleotides and nanoparticles in the second aqueous solution for an additional period of time to enable additional oligonucleotides to bind to the nanoparticles (Mirkin et al. teach contacting the oligonucleotides and nanoparticles in the second solution for an additional period of time to allow additional oligonucleotides to bind to the nanoparticles (col. 48, lines 63-67).).

Regarding claim 56, Mirkin et al. teach oligonucleotides comprising functional groups which can bind to nanoparticles (col. 48, lines 15-24).

Regarding claim 57, Mirkin et al. teach addition of salt to water in a single batch (col. 48, line 42).

Regarding claim 58, Mirkin et al. teach addition of salt to water gradually over time (col. 48, lines 43-46).

Regarding claims 59 and 60, Mirkin et al. teach salts selected from the group consisting of sodium chloride, magnesium chloride, potassium chloride, ammonium chloride, sodium acetate, ammonium acetate or a combination of two or more of these salts in phosphate buffer (col. 48, lines 36-40).

Regarding claims 52 and 61, Mirkin et al. teach oligonucleotide surface density of at least 10 picomoles/cm^2 (col. 49, line 24).

Regarding claims 53 and 62, Mirkin et al. teach oligonucleotide surface density of at least 15 picomoles/cm^2 (col. 49, lines 26, 27).

Regarding claims 54 and 63, Mirkin et al. teach oligonucleotide surface density of at least 15 picomoles/cm^2 to no greater than about 35-40 picomoles/cm^2 (col. 49, lines 26-32).

Regarding claims 65 and 66, Mirkin et al. teach $HauCl_4$ (col. 51, lines 20, 21).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have used the salt addition method of Mirkin et al. in the production of nanoparticle-oligonucleotide conjugates of Abbott et al. The motivation to do so, provided by Mirkin et al., would have been that conjugates produced by addition of salt solutions ("aging step") were more stable than those produced without the aging step and the process resulted in increased oligonucleotide density (col. 49, lines 8-39). Further, as stated by Mirkin et al., "Aside from their stability, the nanoparticle-oligonucleotide conjugates made by this method exhibit other remarkable properties. See, e.g., Examples 5, 7, and 19 of the present application. In particular, due to the high surface density of the conjugates, they will assemble into large aggregates in the presence of a target nucleic acid or oligonucleotide. The temperature over which the aggregates form and dissociate has unexpectedly been found to be quite narrow, and this unique feature has important practical consequences. In particular, it increases the selectivity and sensitivity of the methods of detection of the present invention. A single base mismatch and as little as 20 femtomoles of target can be detected using the conjugates. Although these features were originally discovered in assays performed in solution, the advantages of the use of these conjugates have been found to extend to assays performed on substrates, including those in which only a single type of conjugate is used."

It would have been *prima facie* obvious to one of ordinary skill in the art to have used nanoparticle conjugates with oligonucleotide density of at least 10 picomoles/cm^2 or at least 15 picomoles/cm^2 to no greater than about 35-40 picomoles/cm^2 of Mirkin et al. in the conjugates of Abbott et al. The motivation to do so, provided by Mirkin et al., would have been that a surface

density of between 10 and 40 picomoles/cm^2 provided stable oligonucleotide conjugates (col. 49, lines 25-32).

Double Patenting

15. A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

16. Claims 37-51 are provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 40-47 and 50-55 of copending Application No. 10/153,483. This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

17. Claims 37, 38, 40 and 42-46 are provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 3-10 of copending Application No. 10/397,579. Even though claim 37 differs from claim 3 of the Application No. 10/397,579 by a limitation of the core not exhibiting a red shift, this is an inherent property of the core, therefore the two claims claim the same invention. This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

18. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

19. Claims 69-71 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 32-34 of copending Application No. 10/397,579. Although the conflicting claims are not identical, they are not patentably distinct from each other because the only difference between claims 69-71 of the instant application and claims 32-34 of the 10/397,579 application is the limitation of the core of the nanoparticle being magnetic. As the nanoparticles are being used in the magnetic field, this is an obvious limitation.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

20. No references were found teaching or suggesting claim 42, but it is rejected for reasons given above.

Conclusion

21. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Teresa E Strzelecka whose telephone number is (571) 272-0789. The examiner can normally be reached on M-F (8:30-5:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

TS
December 14, 2004

JEFFREY FREDMAN
PRIMARY EXAMINER